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INVENTORS: MICHAEL R.S. HILL
SCOTT E. JAHNS
JAMES R. KEOGH

TITLE: METHOD AND SYSTEM FOR DELIVERY OF VASOACTIVE DRUGS TO THE HEART PRIOR TO AND DURING A MEDICAL PROCEDURE

ATTORNEYS: FRANK C. NICHOLAS
CARDINAL LAW GROUP
1603 ORRINGTON AVENUE - SUITE 2000
EVANSTON, ILLINOIS 60201
(847) 905-7111

METHOD AND SYSTEM FOR DELIVERY OF VASOACTIVE DRUGS TO THE HEART PRIOR TO AND DURING A MEDICAL PROCEDURE

PRIORITY

This application claims priority as a continuation to United States Patent Application 10/408,647 filed April 7, 2003, which claims priority to United States Patent Application 09/670440, filed September 26, 2000. The entirety of United States Patent Application 10/408,647 and United States Patent Application 09/670440 is hereby incorporated by reference.

FIELD OF THE INVENTION

This invention relates to methods for performing a medical procedure, especially a procedure during which it is desirable to provide the delivery of drugs to an organ. More particularly, this invention relates to methods and systems of delivering drugs to the heart during a medical procedure in which the beating of a heart is modified to allow the procedure to be performed or to allow blood flow to be controlled.

BACKGROUND OF THE INVENTION

The current leading cause of death in the United States is coronary artery disease in which the coronary arteries are blocked by atherosclerotic plaques or deposits of fat. The typical treatment to relieve a partially or fully blocked coronary artery is coronary artery bypass graph (CABG) surgery.

CABG surgery, also known as "heart bypass" surgery, generally entails using a graph to bypass the coronary obstruction. The procedure is generally lengthy, traumatic and subject to patient risks. Among the risk factors involved is the use of a cardiopulmonary bypass circuit, also known as a "heart-lung machine", to pump blood and oxygenate the blood so that the patient's heart may be stopped during the surgery.

Conventional CABG procedures are typically conducted on a stopped heart while the patient is on a cardiopulmonary bypass circuit.

One method for facilitating coronary bypass surgery on a beating heart includes stimulating the vagal nerve electrically in order to temporarily stop or substantially reduce the beating of the heart. This may be followed by pacing the heart to start or substantially increase its beating.

Another method involves stopping the beating of the heart during coronary bypass surgery using electrical stimulation of the vagal nerve in combination with administration of drugs.

Another method involves stopping the beating of the heart during coronary bypass surgery via the local delivery of drugs to the heart in order to temporarily stop the beating of the heart. This is then followed by pacing the heart to start its beating.

Although it is desirable to still the heart for a period of time in order to allow the surgeon to accomplish a required task without interference from heart movement , i.e. a motionless operative field, is it undesirable to have the heart stopped for too long a period of time since the body needs a constant supply of oxygen. In fact, it is particularly important to maintain sufficient blood flow, and therefore oxygen flow, to the brain. Thus, stopping the heart for prolonged periods of time may cause damage to the patient.

In addition, the field in which the invention is to be performed, i.e. an area of the heart, is typically limited in size. In particular, when surgery is performed on a particular blood vessel, the vessel's size is usually quite small and a great deal of precision is required to perform the surgery or even to locate the vessel. Such precision requires more time during which the heart is stopped.

It would be desirable therefore to provide a method for controllably stopping or slowing the heart intermittently in order to control blood flow during a medical procedure.

It would further be desirable to provide a method for changing the size and shape of desired blood vessels during medical procedure.

It would further be desirable to provide a method for facilitating the location of desired blood vessels during medical procedure.

It would further be desirable to provide a method of delivering drugs to the desired location during a medical procedure.

SUMMARY OF THE INVENTION

One aspect of the present invention provides a method of performing a medical procedure. A first vasoactive substance is delivered to a site of a medical procedure. The medical procedure is then performed. A second vasoactive substance is then delivered to the site. The first vasoactive substance may be a vasodilator such as an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine, a dopamine D1-like receptor agonist, a dopamine D1-like receptor stimulant, and a dopamine D1-like receptor activator. The second vasoactive substance may be a vasoconstrictor such as a sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, an alpha-receptor agonist, an alpha-receptor stimulant, and an alpha-receptor activator.

At least one systemic drug such as a beta-blocker, a cholinergic agent, a cholinesterase inhibitor, a calcium channel blocker, a sodium channel blocker, a potassium channel agent, adenosine, an adenosine receptor agonist, an adenosine deaminase inhibitor, dipyridamole, a monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, a bradykinin agent, a serotoninergic agonist, an antiarrythmic agent, a cardiac glycoside, a local anesthetic, atropine, a calcium solution, an agent that promotes heart rate, an agent that promotes heart contractions, dopamine, a catecholamine, an inotrope glucagon, a hormone, forskolin, epinephrine, norepinephrine, thyroid hormone, a phosphodiesterase

inhibitor, prostacyclin, prostaglandin and a methylxanthine may also be delivered during the procedure. The systemic drug may be naturally occurring or chemically synthesized.

The medical procedure may be a surgical procedure, a non-surgical procedure, a fluoroscopic procedure, a cardiac procedure, a vascular procedure, a neurosurgical procedure, an electrophysiology procedure, a diagnostic procedure, a therapeutic procedure, an ablation procedure, an endovascular procedure, a liver procedure, a spleen procedure, a pulmonary procedure, an aneurysm repair, an imaging procedure, a CAT scan procedure, a MRI procedure, a pharmacological therapy, a drug delivery procedure, a biological delivery procedure, a genetic therapy, a cellular therapy, a cancer therapy, a radiation therapy, a transplantation procedure, a coronary angioplasty procedure, a stent delivery procedure, an atherectomy procedure, a procedure that requires precise control of cardiac motion, a procedure that requires precise control of bleeding, a non-invasive procedure, a minimally invasive procedure, an invasive procedure, a port-access procedure, an endoscopic procedure, a sternotomy procedure, a thoracotomy procedure and a robotic procedure.

A nerve may also be stimulated to adjust the beating of a heart to a first condition. Stimulation of the nerve may be reduced to adjust the beating of a heart to a second condition. The heart may be stimulated to adjust the beating of a heart to a second condition.

Another aspect of the present invention provides a method of performing a medical procedure on a vessel in a heart. A nerve is stimulated to adjust the beating of a heart to a first condition. A first vasoactive substance is delivered to the vessel. The medical procedure is performed on the vessel. A second vasoactive substances is delivered to the vessel. The heart is stimulated to adjust the beating of a heart to a second condition. The nerve may be stimulated a subsequent time to re-adjust beating of the heart to the first condition the procedure may be continued. The nerve may be a vagal nerve, a carotid sinus

nerve, a fat pad. The first vasoactive substance may be a vasodilator such as an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine, a dopamine D1-like receptor agonist, a dopamine D1-like receptor stimulant, and a dopamine D1-like receptor activator. The second vasoactive substance may be a vasoconstrictor such as a sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, an alpha-receptor agonist, an alpha-receptor stimulant, and an alpha-receptor activator.

Another aspect of the present invention provides a method of harvesting a vessel. A nerve is stimulated to adjust beating of a heart to a first condition. A vasodilative substance is delivered to the heart and the vessel is harvested. A vasoconstrictive substance is then delivered to the heart and the heart is stimulated to adjust its beating to a second condition.

Another aspect of the present invention provides a system for performing a medical procedure. The system includes drug delivery means to deliver vasoactive substances to a site of the medical procedure, a transvenous nerve stimulator in communication with the drug delivery means to inhibit beating of a heart and a cardiac stimulator in communication with the drug delivery means to stimulate beating of the heart. The drug delivery means may be a spray, a cream, an ointment, a medicament, a pill, a patch, a catheter, a cannula, a needle and syringe, a pump, and an iontophoretic drug delivery device. The drug may be an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine, a dopamine D1-like receptor agonist, a dopamine D1-like

receptor stimulant, a dopamine D1-like receptor activator, a sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, an alpha-receptor agonist, an alpha-receptor stimulant, and an alpha-receptor activator. The drug may be naturally occurring or chemically synthesized.

Another aspect of the present invention provides a system for performing a medical procedure. The system includes drug delivery means to deliver vasoactive substances to a site of the medical procedure, a transvenous nerve stimulator in communication with the drug delivery means to inhibit beating of a heart and a cardiac stimulator in communication with the drug delivery means to stimulate beating of the heart.

The drug delivery means may be a spray, a cream, an ointment, a medicament, a pill, a patch, a catheter, a cannula, a needle and syringe, a pump, and an iontophoretic drug delivery device. The drug may be an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine, a dopamine D1-like receptor agonist, a dopamine D1-like receptor stimulant, a dopamine D1-like receptor activator, a sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, an alpha-receptor agonist, an alpha-receptor stimulant, and an alpha-receptor activator. The drug may be naturally occurring or chemically synthesized.

The nerve stimulator may stimulated a nerve such as a vagal nerve, a carotid sinus nerve, a fat pad. The nerve stimulator may be, for example, one or more electrodes such as nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes and probe electrodes.

The cardiac stimulator may be, for example, one or more electrodes such as cardiac stimulation electrodes, clip electrodes, needle electrodes, probe electrodes, pacing electrodes, epicardial electrodes, patch electrodes, intravascular electrodes, balloon-type electrodes, basket-type electrodes, tape-type electrodes, umbrella-type electrodes, suction-type electrodes, endotracheal electrodes, endoesophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes and cuff electrodes.

Another aspect of the present invention provides a device for delivering vasoactive substances during a medical procedure. The device includes a processor, a vasoactive delivery component operatively connected to the processor; and a nerve stimulation electrode operatively connected to the processor. The processor processes output from the nerve stimulation electrode and automatically delivers vasoactive substances based on output from the nerve stimulation electrode. The nerve stimulation electrode may be one or more electrodes such as endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, tape-type electrodes, suction-type electrodes, screw-type electrodes, barb-type

electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes and probe electrodes.

The device may also include a cardiac stimulation electrode. The processor processes output from the cardiac stimulation electrode and automatically delivers vasoactive substances based on output from the cardiac stimulation electrode. The cardiac stimulation electrode may be one or more electrodes such as clip electrodes, needle electrodes, probe electrodes, pacing electrodes, epicardial electrodes, patch electrodes, intravascular electrodes, balloon-type electrodes, basket-type electrodes, tape-type electrodes, umbrella-type electrodes, suction-type electrodes, endotracheal electrodes, endoesophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes and cuff electrodes.

The device may also include a breathing regulation electrode for controlling breathing. The processor adjusts the output from the breathing regulation electrode. The breathing regulation electrode may be one or more electrodes such as nerve stimulation electrodes, endotracheal electrodes, endoesophageal electrodes, intravascular electrodes, transcutaneous electrodes, intracutaneous electrodes, balloon-type electrodes, basket-type electrodes, umbrella-type electrodes, suction-type electrodes, screw-type electrodes, tape-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes, patch electrodes, cuff electrodes, clip electrodes, needle electrodes and probe electrodes.

The device may also include a drug pump for delivering at least one systemic drug. The processor adjusts the output of the drug.

The foregoing, and other, features and advantages of the invention will become further apparent from the following detailed description of the presently preferred embodiments, read in conjunction with the accompanying drawings. The detailed description and drawings are merely illustrative of the invention rather than limiting, the scope of the invention being defined by the appended claims in equivalence thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic view of one embodiment of a system for delivering vasoactive drugs during a medical procedure in accordance with the present invention;

FIG. 2 is a schematic view of one embodiment of a medical device in accordance with the present invention;

FIG. 3 is a flow diagram of one embodiment of a method of performing a medical procedure in accordance with the present invention; and

FIG. 4 is a timeline view of one embodiment of a system for delivering vasoactive drugs during a medical procedure in accordance with the present invention.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

FIG. 1 shows a schematic view of one embodiment of a system for performing a medical procedure in accordance with the present invention at **100**. System **100** comprises a vasoactive drug delivery system **7**, a nerve stimulator **10**, and a cardiac stimulator **20**. System **100** may also feature a controller **30** and a breathing regulator **40**.

Drug delivery system **7** preferably includes a vasodilative delivery component **17** and a vasoconstrictive delivery component **27**. Both delivery components **17**, **27** may be any suitable means for delivering drugs to a site of a medical procedure. For example drug delivery system **7** may be a system for delivering a vasodilative spray **17** and a vasoconstrictive spray **27**. Drug delivery system **7** may be a system for delivering a vasodilative cream and a vasoconstrictive cream. Drug delivery system **7** may also be a system for delivering any vasodilative formulation **17** such as an ointment or medicament etc. and any vasoconstrictive formulation **27** such as an ointment or medicament etc. or any combination thereof.

Drug delivery system **7** may comprise a catheter, such as a drug delivery catheter or a guide catheter, for delivering a vasodilative substance **17** followed by a vasoconstrictive substance **27**. A drug delivery catheter may include an expandable member, e.g., a low-pressure balloon, and a shaft having a distal portion, wherein the expandable member is disposed along the distal portion. A catheter for drug delivery may comprise one or more lumens and may be delivered endovascularly via insertion into a blood vessel, e.g., an artery such as a femoral, radial, subclavian or coronary artery. The catheter can be guided into a desired position using various guidance techniques, e.g., flouroscopic guidance and/or a guiding catheter or guide wire techniques. In one embodiment, one catheter is used to deliver both the vasodilative component and the vasoconstrictive component. Drug delivery system **7** may also be a patch, such as a transepicardial patch that slowly releases drugs directly into the myocardium, a cannula, a pump and/or a hypodermic needle and syringe assembly.

Drug delivery system **7** may also be an iontophoretic drug delivery device placed on the heart. In general, the delivery of ionized drugs may be enhanced via a small current applied across two electrodes. Positive ions may be introduced into the tissues from the positive pole, or negative ions from the negative pole. The use of iontophoresis may markedly facilitate the transport of certain ionized drug molecules. For example, lidocaine hydrochloride may be applied to the heart via a drug patch comprising the drug. A positive electrode could be placed over the patch and current passed. The negative electrode would contact the heart or other body part at some desired distance point to complete the circuit.

Drug delivery system **7** may be any suitable system for delivering a vasodilative component followed by a vasoconstrictive component or for delivering any appropriate vasoactive formulation.

A vasodilative component **17** may comprise one or more vasodilative drugs in any suitable formulation or combination. Examples of vasodilative drugs include, but are not limited to, a vasodilator, an organic nitrate, isosorbide mononitrate, a mononitrate, isosorbide dinitrate, a dinitrate, nitroglycerin, a trinitrate, minoxidil, sodium nitroprusside, hydralazine hydrochloride, nitric oxide, nicardipine hydrochloride, fenoldopam mesylate, diazoxide, enalaprilat, epoprostenol sodium, a prostaglandin, milrinone lactate, a bipyridine and a dopamine D1-like receptor agonist, stimulant or activator. The vasodilative component **17** may include a pharmaceutically acceptable carrier or solution in an appropriate dosage. Pharmaceutically acceptable carriers include a number of solutions, preferably sterile, for example, water, saline, Ringer's solution and/or sugar solutions such as dextrose in water or saline. Other possible carriers that may be used include sodium citrate, citric acid, amino acids, lactate, mannitol, maltose, glycerol, sucrose, ammonium chloride, sodium chloride, potassium chloride, calcium chloride, sodium lactate, and/or sodium bicarbonate. Carrier solutions may or may not be buffered. The vasodilative component **17** may

include antioxidants or preservatives such as ascorbic acid. They may also be in a pharmaceutically acceptable form for parenteral administration, for example to the cardiovascular system, or directly to the heart, such as intracoronary infusion or injection. Drug formulations or compositions may comprise agents that provide a synergistic effect when administered together. A synergistic effect between two or more drugs or agents may reduce the amount that normally is required for therapeutic delivery of an individual drug or agent. Two or more drugs may be administered, for example, sequentially or simultaneously. Drugs may be administered via one or more bolus injections and/or infusions or combinations thereof. The injections and/or infusions may be continuous or intermittent.

The vasoconstrictive component **27** may comprise one or more suitable vasoconstrictive drugs in any suitable formulation or combination. Examples of vasoconstrictive drugs include, but are not limited to, a vasoconstrictor, a sympathomimetic, methoxamine hydrochloride, epinephrine, midodrine hydrochloride, desglymidodrine, and an alpha-receptor agonist, stimulant or activator. The vasoconstrictive component **27** may include a pharmaceutically acceptable carrier or solution in an appropriate dosage. Pharmaceutically acceptable carriers include a number of solutions, preferably sterile, for example, water, saline, Ringer's solution and/or sugar solutions such as dextrose in water or saline. Other possible carriers that may be used include sodium citrate, citric acid, amino acids, lactate, mannitol, maltose, glycerol, sucrose, ammonium chloride, sodium chloride, potassium chloride, calcium chloride, sodium lactate, and/or sodium bicarbonate. Carrier solutions may or may not be buffered. The vasoconstrictive component **27** may include antioxidants or preservatives such as ascorbic acid. They may also be in a pharmaceutically acceptable form for parenteral administration, for example to the cardiovascular system, or directly to the heart, such as intracoronary infusion or injection. Drug formulations or compositions may comprise agents that provide a synergistic effect when

administered together. A synergistic effect between two or more drugs or agents may reduce the amount that normally is required for therapeutic delivery of an individual drug or agent. Two or more drugs may be administered, for example, sequentially or simultaneously. Drugs may be administered via one or more bolus injections and/or infusions or combinations thereof. The injections and/or infusions may be continuous or intermittent.

All or a portion of drug delivery system **7** may be placed in any suitable manner for application of drugs to the heart. In one embodiment, system **7** is placed to deliver drugs directly to a vessel of the heart. Drug delivery system **7** may be placed invasively or non-invasively. In one embodiment, all or a portion of drug delivery system **7** is implanted adjacent the target area of the heart. Alternatively, all or a portion of drug delivery system **7** is removably applied to the target area of the heart. For example, system **7** may comprise a vasodilative cream manually applied to the target site followed by a vasoconstrictive spray manually applied to the site. Alternatively, system **7** may comprise a guidable or steerable mechanism, such as a catheter, which allows its position to be adjusted during the medical procedure. System **7** may be positioned endoscopically and other suitable placements of system **7**, such as on or near a target coronary artery and/or vein, a pulmonary artery and/or vein, the right atrium and/or ventricle, the left atrium and/or ventricle, the aorta, the AV node, and/or the coronary sinus. System **7** may also be positioned to administer or deliver drugs via intravenous, intracoronary and/or intraventricular administration in a suitable carrier. Examples of arteries that may be used to deliver drugs to the AV node include the AV node artery, the right coronary artery, the right descending coronary artery, the left coronary artery, the left anterior descending coronary artery and Kugel's artery.

All or a portion of drug delivery system **7** may also be placed in any suitable manner for application of drugs to another area of the body such as the leg or another limb. For example, the system **7** may be placed to apply vasoactive substances to a saphenous vein to be harvested or to any other suitable graft vessel. In one embodiment, system **7** is placed to deliver drugs directly to a suitable graft vessel. Drug delivery system **7** may be placed invasively or non-invasively. In one embodiment, drug delivery system **7** is implanted adjacent the graft vessel. Alternatively, drug delivery system is removably applied to the graft vessel.

Drug delivery system **7** may be powered by AC current, DC current or it may be battery powered by a disposable or re-chargeable battery. Drug delivery system **7** may comprise a surgeon controlled switch box. A switch, or all of drug delivery system **7** may also be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for delivery of drugs by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies.

A visual and/or audible signal used to alert a surgeon to the completion or resumption of vasodilative or vasoconstrictive drugs may be incorporated into system **7**. For example, a beeping tone or flashing light may be used to indicate that a vasodilative drug is being delivered followed by a different tone or light to indicate that a vasoconstrictive drug is being delivered.

Drug delivery system **7** may be slaved to nerve stimulator **10** or cardiac stimulator **20**. Software controlling drug delivery system may be designed to automatically deliver drugs while nerve stimulator **10** or cardiac stimulator **20** is on.

As mentioned above, system **100** may also include a nerve stimulator **10**. In one embodiment, the nerve stimulator **10** may be used to electrically manipulate cardiac rhythm by stimulating the vagus nerve. This vagal stimulation may produce asystole (slowing or stopping of the heart's beating.) Once this induced asystole is stopped, i.e. once the vagal stimulation is stopped, the heart may be allowed to return to its usual cardiac rhythm. Alternatively, the heart may be paced with an electrical pacing system, thereby maintaining a normal cardiac output. Electrical pacing may be selectively and intermittently stopped to allow a surgeon to perform a surgical procedure during asystole.

It is known that stimulation of the vagus nerve can reduce the sinus rate, as well as prolong AV conduction time or, if stimulation energies are high enough, induce AV node block. Use of vagal nerve stimulation to treat supraventricular arrhythmias and angina pectoris is disclosed in the article "Vagal Tuning" by Bilgutay et al., Journal of Thoracic and Cardiovascular Surgery, Vol. 56, No. 1, July, 1968, pp. 71-82. It is also known that stimulation of the carotid sinus nerve produces a similar result, as disclosed in the article "Carotid Sinus Nerve Stimulation in the Treatment of Angina Pectoris and Supraventricular Tachycardia" by Braunwald et al., published in California Medicine, Vol. 112, pp. 41-50, March, 1970.

As set forth in "Functional Anatomy of the Cardiac Efferent Innervation" by Randall et al., in Neurocardiology, edited by Kulbertus et al, Futura Publishing Co., 1988, direct surgical excision of the fat pad associated with the SA node affects the functioning of the SA node without significantly affecting the AV node. Similarly, excision of the fat pad associated with the AV node affects functioning of the AV node without significantly affecting the SA node.

As set forth in the article "Parasympathetic Postganglionic Pathways to the Sinoatrial Node", Bluemel et al., Am. J. Physiol. 259, (Heart Circ. Physiol. 28) H1504-H1510, 1990, stimulation of the fat pad associated with the SA node results in slowing of the sinus rate without the accompanying prolongation of AV conduction time which normally results from vagal nerve stimulation. The article also indicates that stimulation of the fat pad associated with the AV node is believed to produce corresponding effects limited to the AV node, i.e., extension of the AV conduction time without concurrent slowing of the sinus rate.

As set forth in the article "Neural Effects on Sinus Rate and Atrial Ventricular Conduction Produced by Electrical Stimulation From a Transvenous Electrode Catheter in the Canine Right Pulmonary Artery" by Cooper et al., published in Circulation Research, Vol. 46, No. 1, January, 1980, pp. 48-57, the fat pads associated with both the AV node and the SA node may be stimulated by means of electrodes located in the right pulmonary artery. The results obtained include both a depression of the sinus rate and a prolongation of the AV conduction time in response to continuous stimulation at 2-80 Hz at up to 50 ma.

Generally in healthy individuals, the SA node functions as the pacemaker. Normal heart rhythm associated with the SA node is typically referred to as sinus rhythm. When the SA node fails, the AV node generally takes over creating a heart rate of approximately 35 to 60 beats per minute. Heart rhythm associated with the AV node is typically referred to as nodal rhythm. When the AV node itself is blocked or injured, a new even slower pacemaker site may form at the junction of the AV node and the His bundle. Heart rhythm associated with this junction is typically referred to as junctional escape rhythm. When this junction site is inhibited, the Purkinje fibers in the His bundle or below may act as a pacemaker creating a heart rate of approximately 30 beats per minute. Heart rhythm associated with the Purkinje fibers is typically referred to as idioventricular rhythm.

In one embodiment of the present invention, nerve stimulator **10** may be used to electrically manipulate cardiac rhythm by stimulating the carotid sinus nerve, the fat pad associated with the SA node, the fat pad associated with the AV node, the junction of the AV node and the His bundle and/or the Purkinje fibers.

In one embodiment of the present invention, nerve stimulator **10** is used alone or in combination with other heart rate inhibiting agents to temporarily stop or slow the beating heart, thereby eliminating or reducing heart motion and/or blood flow during a medical procedure. For example, the present invention may be used to eliminate or reduce motion in the anastomosis field during CABG procedures such that a facilitated anastomosis procedure may be performed safely and effectively. The number of occasions that the vagal nerve will be stimulated depends on the type of medical procedure to be performed. Likewise, the type of medical procedure to be performed will dictate the duration of the individual electrical stimulations.

Nerve stimulator **10** may be powered by AC current, DC current or it may be battery powered by a disposable or re-chargeable battery. Nerve stimulator **10** may be configured to synchronize activation and deactivation of breathing regulator **40** with vagal stimulation, thereby minimizing or eliminating unwanted heart and chest motion associated with the patient's breathing. Nerve stimulator **10** may comprise a surgeon controlled switch box. A switch may also be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for regulation of the nerve stimulator **10** by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies.

A visual and/or audible signal used to alert a surgeon to the completion or resumption of vagal nerve stimulation may be incorporated into nerve stimulator **10**. For example, a beeping tone or flashing light that increases in frequency as the nerve stimulation period should end or begin may be used.

Nerve stimulator **10** may be slaved to cardiac stimulator **20** or a cardiac stimulator **20** may be slaved to nerve stimulator **10**. For example, the output of cardiac stimulator **20** may be off whenever the output of nerve stimulator **10** is on. Software controlling cardiac stimulator **20** may be designed to automatically commence cardiac pacing if the heart does not resume beating within a pre-determined interval after cessation of vagal nerve stimulation. In addition, the software controlling nerve stimulator **10** may be designed to automatically stop vagal nerve stimulation if the heart has been stopped for too long.

System **100** may also include a cardiac stimulator **20** which may be used to stimulate the heart as desired. As with nerve stimulator **10**, cardiac stimulator **20** may be intermittently stopped and started to allow the surgeon to perform individual steps of a medical procedure.

Cardiac stimulator **20** may be a conventional ventricular demand pacer or dual chamber (atrial-ventricular) pacer. Cardiac stimulator **20** may be powered by AC current, DC current or it may be battery powered by a disposable or re-chargeable battery. Cardiac stimulator **20** may be configured to synchronize activation and deactivation of breathing regulator **40** with pacing, thereby minimizing or eliminating unwanted heart and chest motion associated with the patient's breathing. Cardiac stimulator **20** may be any conventional pacing device suitable for ventricular demand pacing and having leads electrically coupled to a switch box. Cardiac stimulator **20** may be combined in a single unit with a switch box. A switch may also be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon for regulation of the cardiac stimulator by the surgeon. The switch may be, for example, a hand switch, a foot switch, or a voice-activated switch comprising voice-recognition technologies.

A visual and/or audible signal used to prepare a surgeon for the resumption of pacing may be incorporated into cardiac stimulator **20**. For example, a beeping tone or flashing light that increases in frequency as the interruption period ends may be used.

Drug delivery system **7**, nerve stimulator **10** and/or cardiac stimulator **20** may be slaved to a robotic system or a robotic system may be slaved to drug delivery system **7**, nerve stimulator **10** and/or cardiac stimulator **20**. Breathing regulator **40** and other components may also be slaved to such a system. Computer- and voice-controlled robotic systems that position and maneuver endoscopes and/or other surgical instruments for performing microsurgical procedures such as anastomoses through small incisions may be used by a surgeon to perform precise and delicate maneuvers. These robotic systems may allow a surgeon to perform a variety of microsurgical procedures including endoscopic CABG. Endoscopic CABG may allow multiple occluded coronary arteries to be bypassed without a thoracotomy or mini-thoracotomy. Heart valve repair and replacement may also be other surgical applications for these robotic systems. In general, robotic systems may include head-mounted displays that integrate 3-D visualization of surgical anatomy and related diagnostic and monitoring data, miniature high-resolution 2-D and 3-D digital cameras, a computer, a high power light source and a standard video monitor.

System **100** may also include a breathing regulator **40**. In one embodiment, the breathing regulator **40** may be used to stimulate the phrenic nerve in order to provide a diaphragmatic pacemaker. Breathing regulator **40** may comprise one or more electrodes for supplying electrical current to the phrenic nerve to control breathing during vagal and/or cardiac stimulation and/or destimulation. Electrodes used to stimulate the phrenic nerve may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. The application of an electrical stimulus to the phrenic nerve may include, but is not limited to bipolar and/or monopolar techniques. Different electrode positions are accessible through various access openings, for example, in the cervical or thorax regions. Nerve stimulation electrodes may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision, placed on the skin or in

combinations thereof. The present invention may include various electrodes, catheters and electrode catheters suitable for phrenic nerve stimulation to control breathing.

Phrenic nerve stimulation electrodes may be intravascular, patch-type, balloon-type, basket-type, umbrella-type, tape-type, cuff-type, suction-type, screw-type, barb-type, bipolar, monopolar, metal, wire, endotracheal, endoesophageal, intravascular, transcutaneous or intracutaneous electrodes. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the nerve stimulation electrodes. For example, a catheter comprising one or more wire, metal strips or metal foil electrodes or electrode arrays may be used. The catheter may comprise, for example, a balloon, which may be inflated with air, or liquid to press the electrodes firmly against a vessel wall that lays adjacent the phrenic nerve.

Phrenic nerve stimulation electrodes may be oriented in any fashion along the catheter device, including longitudinally or transversely. Various techniques such as ultrasound, fluoroscopy and echocardiography may be used to facilitate positioning of the electrodes. If desired or necessary, avoidance of obstruction of blood flow may be achieved with notched catheter designs or with catheters, which incorporate one or more tunnels or passageways.

In another embodiment, the breathing regulator **40** may comprise a connector, which interfaces with a patient's respirator, and sends a logic signal to activate or deactivate the respirator to control breathing during vagal and/or cardiac stimulation and/or destimulation.

FIG. 2 shows one embodiment of the present invention at **200**. In this embodiment, the elements named above may be combined or connected to a control unit along with other components. The unit **200** may be used to coordinate the various elements. Unit **200** may incorporate a controller or any suitable processor **230**.

Drug delivery system **207** may be incorporated into unit **200**. For example, **FIG. 2** shows drug delivery system **207**, including a vasodilative needle assembly **217** for delivery of vasodilative drugs and a vasoconstrictive needle assembly **227** for delivery of vasoconstrictive drugs. Different positions of the vasodilative component **217** and vasoactive component **227** are accessible through various access openings, for example, in the cervical or thorax regions. Drug delivery system **207** or components of drug delivery system may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the neck or chest, through the internal jugular vein, the esophagus, the trachea, placed on the skin or in combinations thereof.

Drug delivery system **207** may be in communication with a processor **230** as shown in **FIG. 2**. The processor may thus be used to process the administration of drugs delivered by system **207**. The processor may store information about the drugs being delivered such as dosage amounts and when particular dosages have been delivered.

Unit **200** may also incorporate a nerve stimulator. For example, **FIG. 2** shows an electrode for nerve stimulation at **210**. Electrodes used to stimulate a nerve such as the vagal nerve may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. The application of an electrical stimulus to the right or left vagal nerve may include, but is not limited to bipolar and/or monopolar techniques. Different electrode positions are accessible through various access openings, for example, in the cervical or thorax regions. Nerve stimulation electrodes **210** may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the neck or chest, through the internal jugular vein, the esophagus, the trachea, placed on the skin or in combinations thereof. Electrical stimulation may be carried out on the right vagal nerve, the left vagal nerve or to both nerves simultaneously or sequentially. The present

invention may include various electrodes, catheters and electrode catheters suitable for vagal nerve stimulation to temporarily stop or slow the beating heart alone or in combination with other heart rate inhibiting agents.

Nerve stimulation electrodes **210** may be endotracheal, endoesophageal, intravascular, transcutaneous, intracutaneous, patch-type, balloon-type, cuff-type, basket-type, umbrella-type, tape-type, screw-type, barb-type, metal, wire or suction-type electrodes. Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the nerve stimulation electrodes **210**. For example, a catheter comprising one or more wire, metal strips or metal foil electrodes or electrode arrays may be inserted into the internal jugular vein to make electrical contact with the wall of the internal jugular vein, and thus stimulate the vagal nerve adjacent to the internal jugular vein. Access to the internal jugular vein may be via, for example, the right atrium, the right atrial appendage, the inferior vena cava or the superior vena cava. The catheter may comprise, for example, a balloon, which may be inflated with air or liquid to press the electrodes firmly against the vessel wall. Similar techniques may be performed by insertion of a catheter-type device into the trachea or esophagus. Additionally, tracheal tubes and esophageal tubes comprising electrodes may be used.

Nerve stimulation electrodes **210** may be oriented in any fashion along the catheter device, including longitudinally or transversely. Various techniques such as ultrasound, fluoroscopy and echocardiography may be used to facilitate positioning of the electrodes. If desired or necessary, avoidance of obstruction of blood flow may be achieved with notched catheter designs or with catheters, which incorporate one or more tunnels or passageways.

In one embodiment of the present invention, the location of the electrodes **210** is chosen to elicit maximum bradycardia effectiveness while minimizing current spread to adjacent tissues and vessels and to prevent the induction of post stimulation tachycardia. Furthermore, a non-conductive material such as plastic may be employed to sufficiently enclose the electrodes of all the configurations to shield them from the surrounding tissues and vessels, while exposing their confronting edges and surfaces for positive contact with the vagal nerve or selected tissues.

Unit **200** may also incorporate a cardiac stimulator. For example, **FIG. 2** shows an electrode for stimulation of the heart at **220**. Cardiac electrodes **220** used to stimulate the heart may be, for example, non-invasive, e.g., clips, or invasive, e.g., needles or probes. Electrodes **220** may be positioned through a thoracotomy, sternotomy, endoscopically through a percutaneous port, through a stab wound or puncture, through a small incision in the chest, placed on the chest or in combinations thereof. The present invention may also use various electrodes, catheters and electrode catheters suitable for pacing the heart, e.g., epicardial, patch-type, intravascular, balloon-type, basket-type, umbrella-type, tape-type electrodes, suction-type, pacing electrodes, endotracheal electrodes, endoesophageal electrodes, transcutaneous electrodes, intracutaneous electrodes, screw-type electrodes, barb-type electrodes, bipolar electrodes, monopolar electrodes, metal electrodes, wire electrodes and cuff electrodes. . Guided or steerable catheter devices comprising electrodes may be used alone or in combination with the electrodes.

Controller **230** may thus be used to gather information from drug delivery system **207**, nerve stimulation electrodes **210** and cardiac stimulation electrodes **220**. Controller **230** may also be used to control the stimulation levels and stimulation duration of nerve stimulation electrodes **210** and cardiac stimulation electrodes **220** or the drug delivery levels and duration of system **207**. Controller **230** may also gather and process information from the various components of system **100**. This information may be used to adjust stimulation levels and stimulation times of nerve stimulation electrodes **210** and cardiac stimulation electrodes **220** or the drug delivery levels and duration of system **207**.

Unit **200** may incorporate one or more switches to facilitate regulation of the various components by the surgeon. Once example of such a switch is shown as foot pedal **250**. The switch may also be, for example, a hand switch, or a voice-activated switch comprising voice-recognition technologies. The switch may be incorporated in or on one of the surgeon's instruments, such as surgical site retractor, or any other location easily and quickly accessed by the surgeon. Unit **200** may also include a display **260**. Unit **200** may also include other means of indicating the status of various components to the surgeon such as a numerical display, gauges, a monitor display or audio feedback. Unit **200** may also include one or more visual and/or audible signals used to prepare a surgeon for the start or stop of nerve stimulation and/or cardiac stimulation.

FIG. 3 shows a flow diagram of one embodiment of the present invention. The patient is prepared for a medical procedure at **500**.

At Block **510**, a nerve that controls the beating of the heart is stimulated. Such a nerve may be for example a vagal nerve. During this time, one or more of a variety of pharmacological agents or drugs may be delivered locally or systemically in addition to the locally administered vasoactive drugs delivered by system **7** at Block **517**. These drugs may produce reversible asystole of a heart while maintaining the ability of the heart to be electrically paced. In one embodiment of the invention, a vasodilator is delivered at Block **517**.

A variety of pharmacological agents or drugs may also be delivered at other times during the procedure **500**. These drugs may also produce reversible asystole of a heart while maintaining the ability of the heart to be electrically paced. Other drugs may be administered for a variety of functions and purposes as described below. Drugs may be delivered at any appropriate time during the medical procedure, for example, at the beginning of the procedure, intermittently during the procedure, continuously during the procedure or following the procedure.

Drugs, drug formulations or compositions suitable for administration to a patient during a medical procedure may include a pharmaceutically acceptable carrier or solution in an appropriate dosage. There are a number of pharmaceutically acceptable carriers that may be used for delivery of various drugs, for example, via direct injection, oral delivery, suppository delivery, transdermal delivery, epicardial delivery and/or inhalation delivery. Pharmaceutically acceptable carriers include a number of solutions, preferably sterile, for example, water, saline, Ringer's solution and/or sugar solutions such as dextrose in water or saline. Other possible carriers that may be used include sodium citrate, citric acid, amino acids, lactate, mannitol, maltose, glycerol, sucrose, ammonium chloride, sodium chloride, potassium chloride, calcium chloride, sodium lactate, and/or sodium bicarbonate. Carrier solutions may or may not be buffered.

Drug formulations or compositions may include antioxidants or preservatives such as ascorbic acid. They may also be in a pharmaceutically acceptable form for parenteral administration, for example to the cardiovascular system, or directly to the heart, such as intracoronary infusion or injection. Drug formulations or compositions may comprise agents that provide a synergistic effect when administered together. A synergistic effect between two or more drugs or agents may reduce the amount that normally is required for therapeutic delivery of an individual drug or agent. Two or more drugs may be administered,

for example, sequentially or simultaneously. Drugs may be administered via one or more bolus injections and/or infusions or combinations thereof. The injections and/or infusions may be continuous or intermittent. Drugs may be administered, for example, to a coronary artery and/or vein, a pulmonary artery and/or vein, the right atrium and/or ventricle, the left atrium and/or ventricle, the aorta, the AV node, and/or the coronary sinus. Drugs may be administered or delivered via intravenous, intracoronary and/or intraventricular administration in a suitable carrier. Examples of arteries that may be used to deliver drugs to the AV node include the AV node artery, the right coronary artery, the right descending coronary artery, the left coronary artery, the left anterior descending coronary artery and Kugel's artery. Besides being delivered locally, drugs may be delivered systemically, for example, via oral, transdermal, intranasal, suppository or inhalation methods. Drugs also may be delivered via a pill, a spray, a cream, an ointment or a medicament formulation.

Drugs may be delivered via a drug delivery device that may comprise a catheter, such as a drug delivery catheter or a guide catheter, a patch, such as a transepicardial patch that slowly releases drugs directly into the myocardium, a cannula, a pump and/or a hypodermic needle and syringe assembly. A drug delivery catheter may include an expandable member, e.g., a low-pressure balloon, and a shaft having a distal portion, wherein the expandable member is disposed along the distal portion. A catheter for drug delivery may comprise one or more lumens and may be delivered endovascularly via insertion into a blood vessel, e.g., an artery such as a femoral, radial, subclavian or coronary artery. The catheter can be guided into a desired position using various guidance techniques, e.g., flouroscopic guidance and/or a guiding catheter or guide wire techniques.

Drugs may be delivered via an iontophoretic drug delivery device placed on the heart. In general, the delivery of ionized drugs may be enhanced via a small current applied across two electrodes. Positive ions may be introduced into the tissues from the positive pole, or negative ions from the negative pole. The use of iontophoresis may markedly facilitate the transport of certain ionized drug molecules. For example, lidocaine hydrochloride may be applied to the heart via a drug patch comprising the drug. A positive electrode could be placed over the patch and current passed. The negative electrode would contact the heart or other body part at some desired distance point to complete the circuit. One or more of the electrodes may also be used as nerve stimulation electrodes **210** or as cardiac stimulation electrodes **220**.

The two divisions of the autonomic nervous system that regulate the heart have opposite functions. First, the adrenergic or sympathetic nervous system increases heart rate by releasing epinephrine and norepinephrine. Second, the parasympathetic system also known as the cholinergic nervous system or the vagal nervous system decreases heart rate by releasing acetylcholine. Catecholamines such as norepinephrine (also called noradrenaline) and epinephrine (also called adrenaline) are agonists for beta-adrenergic receptors. An agonist is a stimulant biomolecule or agent that binds to a receptor.

Beta-adrenergic receptor blocking agents compete with beta-adrenergic receptor stimulating agents for available beta-receptor sites. When access to beta-receptor sites are blocked by receptor blocking agents, also known as beta-adrenergic blockade, the chronotropic or heart rate, inotropic or contractility, and vasodilator responses to receptor stimulating agents are decreased proportionately. Therefore, beta-adrenergic receptor blocking agents are agents that are capable of blocking beta-adrenergic receptor sites.

Since beta-adrenergic receptors are concerned with contractility and heart rate, stimulation of beta-adrenergic receptors, in general, increases heart rate, the contractility of the heart and the rate of conduction of electrical impulses through the AV node and the conduction system.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized (synthetic analogues) beta-adrenergic receptor blocking agents. Beta-adrenergic receptor blocking agents or □-adrenergic blocking agents are also known as beta-blockers or □-blockers and as class II antiarrhythmics.

The term "beta-blocker" appearing herein may refer to one or more agents that antagonize the effects of beta-stimulating catecholamines by blocking the catecholamines from binding to the beta-receptors. Examples of beta-blockers include, but are not limited to, acebutolol, alprenolol, atenolol, betantolol, betaxolol, bevantolol, bisoprolol, carterolol, celiprolol, chlorthalidone, esmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, oxprenolol, sotalol, teratolol, timolol and combinations, mixtures and/or salts thereof.

The effects of administered beta-blockers may be reversed by administration of beta-receptor agonists, e.g., dobutamine or isoproterenol.

The parasympathetic or cholinergic system participates in control of heart rate via the sinoatrial (SA) node, where it reduces heart rate. Other cholinergic effects include inhibition of the AV node and an inhibitory effect on contractile force. The cholinergic system acts through the vagal nerve to release acetylcholine, which, in turn, stimulates cholinergic receptors. Cholinergic receptors are also known as muscarinic receptors. Stimulation of the cholinergic receptors decreases the formation of cAMP. Stimulation of cholinergic receptors generally has an opposite effect on heart rate compared to stimulation of beta-adrenergic receptors. For example, beta-adrenergic stimulation increases heart rate, whereas cholinergic stimulation decreases it. When vagal tone is high and adrenergic tone is low, there is a marked slowing of the heart (sinus bradycardia). Acetylcholine effectively reduces the amplitude, rate of increase and duration of the SA node action potential. During vagal nerve stimulation, the SA node does not arrest. Rather, pacemaker function may shift to cells that fire

at a slower rate. In addition, acetylcholine may help open certain potassium channels thereby creating an outward flow of potassium ions and hyperpolarization. Acetylcholine also slows conduction through the AV node.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized (synthetic analogues) cholinergic agent. The term "cholinergic agent" appearing herein may refer to one or more cholinergic receptor modulators or agonists. Examples of cholinergic agents include, but are not limited to, acetylcholine, carbachol (carbamyl choline chloride), bethanechol, methacholine, arecoline, norarecoline and combinations, mixtures and/or salts thereof.

Drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized cholinesterase inhibitor. The term "cholinesterase inhibitor" appearing herein may refer to one or more agents that prolong the action of acetylcholine by inhibiting its destruction or hydrolysis by cholinesterase. Cholinesterase inhibitors are also known as acetylcholinesterase inhibitors. Examples of cholinesterase inhibitors include, but are not limited to, edrophonium, neostigmine, neostigmine methylsulfate, pyridostigmine, tacrine and combinations, mixtures and/or salts thereof.

There are ion-selective channels within certain cell membranes. These ion selective channels include calcium channels, sodium channels and/or potassium channels. Therefore, other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized calcium channel blocker. Calcium channel blockers inhibit the inward flux of calcium ions across cell membranes of arterial smooth muscle cells and myocardial cells. Therefore, the term "calcium channel blocker" appearing herein may refer to one or more agents that inhibit or block the flow of calcium ions across a cell membrane. The calcium channel is

generally concerned with the triggering of the contractile cycle. Calcium channel blockers are also known as calcium ion influx inhibitors, slow channel blockers, calcium ion antagonists, calcium channel antagonist drugs and as class IV antiarrhythmics. A commonly used calcium channel blocker is verapamil.

Administration of a calcium channel blocker, e.g., verapamil, generally prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner, since the electrical activity through the AV node depends significantly upon the influx of calcium ions through the slow channel. A calcium channel blocker has the ability to slow a patient's heart rate, as well as produce AV block. Examples of calcium channel blockers include, but are not limited to, amiloride, amlodipine, bepridil, diltiazem, felodipine, isradipine, mibefradil, nicardipine, nifedipine (dihydropyridines), nickel, nimodinpine, nisoldipine, nitric oxide (NO), norverapamil and verapamil and combinations, mixtures and/or salts thereof. Verapamil and diltiazem are very effective at inhibiting the AV node, whereas drugs of the nifedipine family have a lesser inhibitory effect on the AV node. Nitric oxide (NO) indirectly promotes calcium channel closure. NO may be used to inhibit contraction. NO may also be used to inhibit sympathetic outflow, lessen the release of norepinephrine, cause vasodilation, decrease heart rate and decrease contractility. In the SA node, cholinergic stimulation leads to formation of NO.

Other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized sodium channel blocker. Sodium channel blockers are also known as sodium channel inhibitors, sodium channel blocking agents, rapid channel blockers or rapid channel inhibitors. Antiarrhythmic agents that inhibit or block the sodium channel are known as class I antiarrhythmics, examples include, but are not limited to, quinidine and quinidine-like agents, lidocaine and lidocaine-like agents, tetrodotoxin, encainide, flecainide and combinations, mixtures and/or salts thereof. Therefore, the term "sodium channel blocker"

appearing herein may refer to one or more agents that inhibit or block the flow of sodium ions across a cell membrane or remove the potential difference across a cell membrane. For example, the sodium channel may also be totally inhibited by increasing the extracellular potassium levels to depolarizing hyperkalemic values, which remove the potential difference across the cell membrane. The result is inhibition of cardiac contraction with cardiac arrest (cardioplegia). The opening of the sodium channel (influx of sodium) is for swift conduction of the electrical impulse throughout the heart.

Other drugs, drug formulations and/or drug compositions that may be used according to this invention may include any naturally occurring or chemically synthesized potassium channel agent. The term "potassium channel agent " appearing herein may refer to one or more agents that impact the flow of potassium ions across the cell membrane. There are two major types of potassium channels. The first type of channel is voltage-gated and the second type is ligand-gated. Acetylcholine-activated potassium channels, which are ligand-gated channels, open in response to vagal stimulation and the release of acetylcholine. Opening of the potassium channel causes hyperpolarization, which decreases the rate at which the activation threshold is reached. Adenosine is one example of a potassium channel opener. Adenosine slows conduction through the AV node. Adenosine, a breakdown product of adenosine triphosphate, inhibits the AV node and atria. In atrial tissue, adenosine causes the shortening of the action potential duration and causes hyperpolarization. In the AV node, adenosine has similar effects and may also decrease the action potential amplitude and the rate of increase of the action potential. Adenosine is also a direct vasodilator by its actions on the adenosine receptor on vascular smooth muscle cells. In addition, adenosine acts as a negative neuromodulator, thereby inhibiting release of norepinephrine. Class III antiarrhythmic agents also known as potassium channel inhibitors lengthen the action potential duration and

refractoriness by blocking the outward potassium channel to prolong the action potential. Amiodarone and d-sotalol are both examples of class III antiarrhythmic agents.

Potassium is the most common component in cardioplegic solutions. High extracellular potassium levels reduce the membrane resting potential. Opening of the sodium channel, which normally allows rapid sodium influx during the upstroke of the action potential, is therefore inactivated because of a reduction in the membrane resting potential. The present invention may be combined with conventional CPB, the induced asystole as described by this invention may serve as a substitute for conventional cardioplegic arrest. For example, the combination of drugs and vagal stimulation may be used as a cardioplegic agent in a variety of medical procedures.

Drugs, drug formulations and/or drug compositions that may be used during according to this invention may comprise one or more of any naturally occurring or chemically synthesized beta-blocker, cholinergic agent, cholinesterase inhibitor, calcium channel blocker, sodium channel blocker, potassium channel agent, adenosine, adenosine receptor agonist, adenosine deaminase inhibitor, dipyridamole, monoamine oxidase inhibitor, digoxin, digitalis, lignocaine, bradykinin agents, serotoninergic agonist, antiarrythmic agents, cardiac glycosides, local anesthetics and combinations or mixtures thereof. Digitalis and digoxin both inhibit the sodium pump. Digitalis is a natural inotrope derived from plant material, while digoxin is a synthesized inotrope. Dipyridamole inhibits adenosine deaminase, which breaks down adenosine. Drugs, drug formulations and/or drug compositions capable of reversibly suppressing autonomous electrical conduction at the SA and/or AV node, while still allowing the heart to be electrically paced to maintain cardiac output may be used according to this invention.

In one embodiment, the cardiac asystole produced in accordance with the present invention is reversible, e.g., chemically such as by the administration of atropine or by natural forces. Beta-adrenergic stimulation or administration of calcium solutions may be used to reverse the effects of a calcium channel blocker such as verapamil. Agents that promote heart rate and/or contraction may be used in a preferred embodiment of the present invention. For example, dopamine, a natural catecholamine, is known to increase contractility. Positive inotropes are agents that specifically increase the force of contraction of the heart. Glucagon, a naturally occurring hormone, is known to increase heart rate and contractility. Glucagon may be used to reverse the effects of a beta-blocker since its effects bypass the beta receptor. Forskolin is known to increase heart rate and contractility. As mentioned earlier, epinephrine and norepinephrine naturally increase heart rate and contractility. Thyroid hormone, phosphodiesterase inhibitors and prostacyclin, a prostaglandin, are also known to increase heart rate and contractility. In addition, methylxanthines are known to prevent adenosine from interacting with its cell receptors.

Typically, vagal nerve stimulation prevents the heart from contracting. This non-contraction must then be followed by periods without vagal nerve stimulation during which the heart is allowed to contract.

At Block **517**, a vasoactive drug is delivered to the site of the medical procedure. In one embodiment, a vasodilative drug is delivered locally using vasodilative delivery component **17**. The drug may be applied directly to a vessel in order to cause the vessel to dilate. Such a dilated vessel is easier to view and provides an enlarged field upon which to perform the procedure.

At Block **520**, a medical procedure may be performed or begun. Such a procedure may be, for example, surgery on the heart. In one embodiment, the procedure may be surgery on the vessel upon which the vasodilative formulation has been delivered. Alternatively, the procedure may be surgery performed on another organ or another vessel in another organ of the body. For example, a graft vessel, such as the saphenous vein, may be harvested at this point.

The term "medical procedure" may mean any one or more medical or surgical procedures such as, for example cardiac surgery, performed with or without cardiopulmonary bypass (CPB) circuits, heart valve repair, heart valve replacement, MAZE procedures, revascularization procedures, transmyocardial revascularization (TMR) procedures, percutaneous myocardial revascularization (PMR) procedures, CABG procedures, anastomosis procedures, non-surgical procedures, fluoroscopic procedures, beating heart surgery, vascular surgery, neurosurgery, brain surgery, electrophysiology procedures, diagnostic and therapeutic procedures, ablation procedures, ablation of arrhythmias, endovascular procedures, treatment of the liver, spleen, heart, lungs, and major blood vessels, aneurysm repair, imaging procedures of the heart and great vessels, CAT scans or MRI procedures, pharmacological therapies, drug delivery procedures, gene therapies, cellular therapies, cancer therapies, radiation therapies, genetic, cellular, tissue and/or organ manipulation or transplantation procedures, coronary angioplasty procedures, placement or delivery of coated or noncoated stents, atherectomy procedures, atherosclerotic plaque manipulation and/or removal procedures, procedures where bleeding needs to be precisely controlled, procedures that require precise control of cardiac motion and/or bleeding.

When the medical procedure comprises one or more medical devices, e.g., coated stents, these devices may be coated with one or more radioactive materials and/or biological agents such as, for example, an anticoagulant agent, an antithrombotic agent, a clotting agent, a platelet agent, an anti-inflammatory agent, an antibody, an antigen, an immunoglobulin, a defense agent, an enzyme, a hormone, a growth factor, a neurotransmitter, a cytokine, a blood agent, a regulatory agent, a transport agent, a fibrous agent, a protein, a peptide, a proteoglycan, a toxin, an antibiotic agent, an antibacterial agent, an antimicrobial agent, a bacterial agent or component, hyaluronic acid, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, a vitamin, a DNA segment, a RNA

segment, a nucleic acid, a lectin, an antiviral agent, a viral agent or component, a genetic agent, a ligand and a dye (which acts as a biological ligand). Biological agents may be found in nature (naturally occurring) or may be chemically synthesized.

The medical procedure may be non-invasive, minimally invasive and/or invasive. The medical procedure may entail a port-access approach, a partial or total endoscopic approach, a sternotomy approach or a thoracotomy approach. The medical procedure may include the use of various mechanical stabilization devices or techniques as well as various robotic or imaging systems.

In one method, the heart may be temporarily slowed or intermittently stopped for short periods of time to permit the surgeon to accomplish the required surgical task and yet still allow the heart itself to supply oxygenated blood to the body. For example, stimulation of the vagus nerve in order to temporarily and intermittently slow or stop the heart is disclosed in U.S. Patent No. 6,006,134 entitled "Method and Device for Electronically Controlling the Beating of a Heart Using Venous Electrical Stimulation of Nerve Fibers", Dec. 21, 1999, to Hill and Junkman. This patent is assigned to Medtronic, Inc. and is incorporated herein by reference.

As seen in **FIG. 3**, an additional vasoactive drug or drug formulation may be delivered to the site of the medical procedure at block **527** in one embodiment of the invention. For example, a vasoconstrictive drug may be delivered locally using vasoconstrictive delivery component **17**. The drug may be applied directly to a vessel in order to cause the vessel to constrict, particularly to constrict to its usual size. Such a constricted vessel may now perform its usual functions.

After a time, the medical procedure or one phase of the procedure is completed. After some phase of the medical procedure is performed, cardiac contractions are allowed to occur (block **530**). Cardiac contractions may need to occur intermittently during the procedure to ensure adequate blood flow. In one embodiment, the stimulation from the nerve stimulator **10** is stopped or slowed enough to allow the heart to contract. For example, the vagal nerve stimulation is removed, thereby allowing cardiac contractions to occur.

In another embodiment, the heart may be stimulated to ensure that cardiac contractions occur (block **535**). For example, cardiac stimulator **20** may be used to apply pacing pulses to the heart to encourage the heart to contract normally. In particular, the pacing pulses may be applied to the ventricle as is well known in the field.

The present invention permits the heart to be stilled for selected and controllable periods of time in order to permit a medical procedure to be performed. While such a period of stillness is desired, it must not last too long, otherwise insufficient blood and oxygen is delivered to organs. Thus, it is necessary to have the periods when the heart is beating (blocks **530**, **535**).

If additional medical procedures or additional stages of medical procedures need to be performed, the heart may again be stilled using the methods of stilling the heart described above. Therefore, from block **530** or block **535**, the method may be repeated (block **540**). For example, the heart may again be prevented from contracting by stimulation of the vagal nerve (**510**). Additional delivery of a vasodilative formulation (block **517**) followed by, for example, surgery (block **520**) followed by delivery of a vasoconstrictive formulation (block **527**) may occur on the same or a different vessel. Additional drugs may be delivered or the drugs previously administered may continue to be administered.

Additional steps of the medical procedure or additional medical procedures may be performed (Block **520**) while the heart is still. Then this stage of stillness may be followed by another stage when the stimulation is removed (block **530**) and the heart is allowed to contract. Again, the heart may be stimulated to encourage contractions (block **535**).

This cycle may be repeated until the procedure, such as surgery, is completed. After the procedure is completed, step **535** may be performed until the heart is beating normally.

For example, a surgical procedure at **520** may require several stitches to be made by the surgeon. The surgeon may stimulate the vagal nerve at **510** to stop the heart. The surgeon may then apply the vasodilative formulation at **517** to facilitate viewing of and manipulation of the vessel to be stitched. Then the surgeon may make the first stitch at **520**. The surgeon may apply a vasoconstrictive formulation if appropriate at **527**. The surgeon may then reduce or halt stimulation at **530** and allow the heart to contract. The surgeon may also pace the heart at **535**. Then at **540**, the surgeon may return to **510** to inhibit contractions of the heart. At **520**, the surgeon will then make the second stitch. This process may be repeated (the loop designated by **540** may be repeated) until all the required stitches have been made. Alternatively, the surgeon may apply the vasocontrictive formulation at block **545** after all the required stitches have been made.

In one embodiment, after the surgery is completed, step **535** is performed until the heart is beating normally. At the procedure's end, one or more of a variety of pharmacological agents or drugs may be delivered or may continue to be delivered for example to alleviate pain or aid in recuperation. Other drugs may be administered for a variety of functions and purposes as described above.

FIG. 4 is a timeline illustrating one embodiment of the relationship between vasoactive drug delivery, vagal nerve stimulation and cardiac stimulation.

Point **610** indicates a point before the medical procedure has begun. At this point **610**, both nerve stimulation and cardiac stimulation are off. At point **610**, the heart is beating regularly. Then nerve stimulation is turned on to inhibit beating of the heart. During phase **601**, the vagal nerve stimulation is on and the cardiac stimulation is off. This is the condition of the two types of stimulation at step **520** described above.

Point **611** is a representative point during phase **601**. At point **611**, the contractions of the heart are stilled or substantially slowed. A vasoactive formulation may be delivered at point **612**, once the heart is still or substantially slowed. After all or a portion of the medical procedure is performed during phase **601**, a vasoconstrictive substance may be delivered at point **613**, which is a point near the end of phase **601**. Alternatively, the vasoconstrictive substance may be applied at a later time.

During phase **602** the vagal stimulation is turned off (as described at step **530**) and the cardiac stimulation may be turned on (as described at **535**). Point **614** is a representative point during phase **602**. At point **614**, the contractions are allowed and/or may be induced.

During phase **603**, the vagal nerve stimulation is again turned on and the cardiac stimulation is turned off. Vasoactive substances may again be delivered during phase **603** in an appropriate manner. The amounts or types of vasoactive substances delivered during phase **603** may be the same or different from those delivered during phase **601**. In one embodiment, phase **603** is the final phase of the medical procedure and at point **615**, which is a point after the medical procedure has been completed, a vasoconstrictive formulation may be delivered.

Alternatively, the procedure may enter a phase represented by phase **604**. During phase **604** the vagal stimulation is again turned off and the cardiac stimulation may again be turned on. Point **616** is a representative point during phase **604**. At point **616**, the contractions are allowed and/or may be induced.

The method of the present invention may be repeated as necessary until a point is reached, represented by point **617**, when the necessary medical procedures are completed. At this point **617**, nerve stimulation is off although cardiac stimulation may be left on in order to pace the heart to its normal rhythm. Vasoconstrictive drugs or other drugs may be delivered at point **617**.

It will be appreciated by those skilled in the art that while the invention has been described above in connection with particular embodiments and examples, the invention is not necessarily so limited, and that numerous other embodiments, examples, uses, modifications and departures from the embodiments, examples and uses are intended to be encompassed by the claims attached hereto. The entire disclosure of each patent and publication cited herein is incorporated by reference, as if each such patent or publication were individually incorporated by reference herein.